

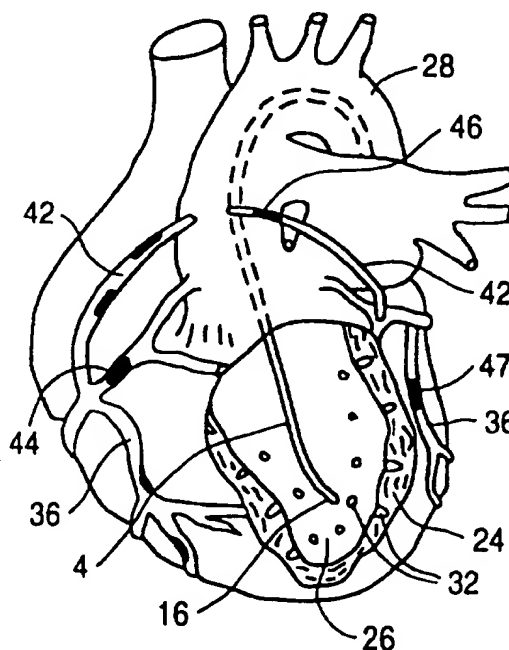


INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ : A61K 9/22	A1	(11) International Publication Number: WO 98/05307 (43) International Publication Date: 12 February 1998 (12.02.98)
(21) International Application Number: PCT/US97/13904 (22) International Filing Date: 7 August 1997 (07.08.97) (30) Priority Data: 60/023,743 8 August 1996 (08.08.96) US 08/906,991 6 August 1997 (06.08.97) US (71) Applicant: LOCALMED, INC. [US/US]; 1820 Embarcadero Road, Palo Alto, CA 94303 (US). (72) Inventors: KAPLAN, Aaron, V.; 851 Carnation Court, Los Altos, CA 94024 (US). ABRAMS, Robert, M.; 359 Redondo Terrace, Sunnyvale, CA 94086 (US). KLEIN, Enrique, J.; 1686 Christina Drive, Los Altos, CA 94024 (US). (74) Agents: HESLIN, James, M. et al.; Townsend and Townsend and Crew LLP, Two Embarcadero Center, 8th floor, San Francisco, CA 94111-3834 (US).	(81) Designated States: AU, CA, IL, JP, KR, NZ, European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE). Published <i>With international search report.</i> <i>Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>	

(54) Title: TRANSMURAL DRUG DELIVERY METHOD AND APPARATUS**(57) Abstract**

A transmural drug delivery method broadly includes the steps of forming a channel through a tissue surface into the tissue and introducing a drug into the channel. A preferred method promotes myocardial angiogenesis by first forming endocardial channels (32) through the endocardium (30) from within the left ventricle (26) and then introducing angiogenic factors into the channel to promote growth of new arterioles (34) within the myocardium (24). The new arterioles connect the channels to each other, to the coronary arteries (36) and grow in the myocardium itself. Doing so supplies the blood from the left ventricle directly to the myocardium and may also provide flow paths around blockages (47) in the coronary arteries to lessen or eliminate myocardial ischemia. The invention can also be used to introduce other agents into myocardial tissue and into the tissue of other organs.



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5 **TRANSMURAL DRUG DELIVERY METHOD AND APPARATUS**

 The present application is a continuation-in-part of
provisional application no. 60/023,743, filed on
August 8, 1997, the full disclosure of which is incorporated
10 herein by reference.

BACKGROUND OF THE INVENTION

1. Field of the Invention

 The present invention relates generally to methods
15 and apparatus for drug delivery. One aspect of the present
invention relates to methods and apparatus for promoting
myocardial angiogenesis to treat ischemia.

 Coronary artery disease usually results from the
deposition of atheromatous plaque in the large and medium-
20 sized arteries supplying the heart. Such blockages of the
coronary arteries can in turn cause myocardial ischemia which
is a condition characterized by inadequate blood flow from the
coronary arteries to heart tissue. In severe cases, coronary
artery disease can lead to myocardial infarction (heart
25 attack) and sudden cardiac death. Angina pectoris is a
chronic condition associated with myocardial ischemia and
characterized by chest discomfort as a result of vigorous and
in some cases even mild exertion.

 Angina pectoris can be treated by the administration
30 of drugs, such as β -adrenergic blocking agents and
vasodilators, including nitroglycerin, amyl nitrite, nitrates,
and calcium antagonists. While effective for short-term
treatment, such drugs are ineffective at treating the arterial
blockages responsible for the underlying coronary artery
35 disease. To treat the arterial blockages, various surgical
and catheter-based therapies have been developed. The most
effective is probably coronary artery bypass surgery, where
bypass grafts are surgically implanted around blockages in the

coronary arteries. While very effective, coronary artery bypass surgery is highly invasive and results in significant patient morbidity and mortality. Catheter-based interventions, such as balloon angioplasty, laser angioplasty, and atherectomy, are considerably less invasive, but are also less effective, frequently suffering from abrupt closure or restenosis following the intervention.

Another method for providing oxygenated blood to myocardial tissue is via artificial channels in the ventricular wall allowing oxygenated blood to travel directly from the left ventricle to the surrounding muscle. Two approaches have been used to create these channels. The first is called TMR (transmyocardial revascularization). This procedure can be performed via either open chest or minimally invasive heart surgery. In either case, the channels are formed from the epicardium completely through the myocardium to permit entry of oxygenated blood from the left ventricle to perfuse the myocardium. These channels are typically formed by application of laser energy but could also be created by direct needle puncture, ultrasound, RF and other energies. A second method is called PMR (percutaneous myocardial revascularization). This method accesses the myocardium percutaneously by means of a catheter to the aorta, retrograde access across the aortic valve and into the left ventricle. In this procedure, endocardium channels are formed through the endocardium but not completely through the myocardium. Whereas the creation of channels by either PMR or TMR is a promising new approach for the treatment of patients with coronary artery disease, these techniques have limitations. The efficacy of these procedures may in part dependant upon persistent channel patency as well as the ability of these channels to connect via collateral vessels with coronary arteries.

For these reasons, it would be desirable to provide methods and means to promote channel patency as well as to facilitate the formation of arterial connections, known as collateral circulation, between channels and/or the coronary arteries. Formation of new blood vessels is commonly referred

to as angiogenesis. It would be particularly desirable to provide methods and systems which allowed for the delivery of active agents such as angiogenic factors during the creation of channels during the PMR and TMR procedures.

5

2. Description of the Background Art

Periadvential and systemic delivery of bFGF to promote angiogenesis in cardiac tissue are described in Cuevas et al. (1993) *Surg. Neurol.* 39:380-384; Selke et al. (1994) *Am. J. Physiol.* 267:H1303-1311; Harada et al. (1994) *J. Clin. Invest.* 94:623-630; Edelman et al. (1993) *Proc. Natl. Acad. Sci. USA* 90:1513-1517; and Whalen et al. (1989) *Growth Factors* 1:157-164. The effect of direct coronary infusion of bFGF into swine hearts is described in Battler et al. (1993) *J. Am. Coll. Cardiol.* 22:2001-2006.

The use of intravascular catheters for delivering particular drugs and classes of drugs is described in U.S. Patent Nos. 5,180,366; 5,171,217; 5,049,132; and 5,021,044; and PCT Publications WO 93/08866 and WO 92/11895. Riessen et al. (1994) *JACC* 23:1234-1244 is a review article discussing the use of catheters and stents for the local delivery of therapeutic agents into the blood vessel wall.

Intramural delivery of angiogenic factors to promote revascularization of cardiac tissue is described in copending application serial no. 08/753,224, assigned to the assignee of the present invention, filed on November 22, 1996, the full disclosure of which is incorporated herein by reference.

Various devices and procedures for forming transmural channels in myocardial tissue are described in the following patents and publications: Peter Wittaker, et al. (1996) *Circulation* 93:143-152; Lawrence I. Deckelbaum (1994) *Lasers in Surgery and Medicine* 15:328-330; Mahmood Mirhoseini et al. (1993) *Journal of Clinical Laser Medicine and Surgery* 11:15-19; P. Walter et al. (1971) *Europ. Surg. Res.* 3:130-138; P.K. Sen et al. (1965) *Journal of Thoracic and Cardiovascular Surgery* 50:181-192; U.S. Patent No. 5,389,096; U.S. Patent No. 4,658,817; WO 94/14383 corresponding to PCT/US92/11002; EP 0515867-A2.

Catheters capable of delivering active agents to an endocardial surface are described in U.S. Patent Nos. 5,531,780; 5,447,533; 5,387,419; 5,324,325; and 5,551,427. The later suggests that growth factors can be delivered to cardiac tissue.

SUMMARY OF THE INVENTION

A transmural drug delivery method for the delivery of angiogenic and other bioactive agents and factors to cardiac tissue broadly includes the steps of forming a plurality of channels at least partly into myocardial, and introducing the angiogenic or other factor into the open channels. The angiogenic factors induced blood vessel growth factors which, together with the open channels, enhance blood flow and/or angiogenesis directly from the ventricular chamber into the cardiac tissue, thus at least partially relieving ischemia in ischemic patients. Collateral vessels are expected to form between the channels and between the channels and the coronary arteries. The formation of collateral vessels provides a substantial network of blood flow paths to enhance blood perfusion directly to the myocardium. Exemplary angiogenic factors include naturally occurring peptides, e.g., vascular endothelial growth factor (VEGF), acidic fibroblast growth factor (aFGF), basic fibroblast growth factor (bFGF) and their derivatives or a combination thereof, and the like. Other active agents include polypeptides, carbohydrates, nucleic acids, gene vectors, genetically modified cells, and the like.

The term angiogenesis refers to the growth of blood vessels in tissue in response to stimuli, particularly in response to administration of an angiogenic factor in the manner described below. In addition to promoting angiogenesis, one or more other agents having different activities can be delivered together with an angiogenic factor(s). For example, anti-arrhythmia agents, beta blockers, nitrates such as nitroglycerine, myocardial growth factors, anti-viral agents and anti-rejection agents can be used.

Other features and advantages of the invention will appear from the following description in which the preferred embodiments have been set forth in detail in conjunction with the accompanying drawings.

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BRIEF DESCRIPTION OF THE DRAWINGS

Fig. 1 is a simplified overall view of a catheter assembly made according to the invention;

10 Fig. 2 shows the catheter of Fig. 1 introduced into the left ventricle of a heart, a portion of the heart broken away to illustrate a series of endocardial channels formed within the myocardium of the heart;

15 Fig. 3A is a simplified enlarged view illustrating growth of new arterioles into the myocardium and between the channels;

Fig. 3B is a view similar to Fig. 3A but shows the growth of new arterioles between the channels and various coronary artery branches, the arterioles of Figs. 3A and 3B being illustrated in two different figures for clarity;

20 Fig. 4 illustrates the distal end of an alternative embodiment of the catheter of Fig. 1;

Fig. 5 illustrates a further alternative embodiment of the invention including an agent delivery needle, shown extended;

25 Fig. 6 illustrates a further embodiment of the invention in which the central lumen is somewhat enlarged to permit the delivery of bioeluting or biodegradable/bioerodible particles into the endocardial channels;

30 Fig. 6A illustrates rod-shaped particles which can be used instead of the spherical particles of Fig. 6;

Fig. 6B illustrates a train of bioeluting tubules for placement into the endocardial channels;

35 Fig. 7 illustrates a further embodiment of the invention in which a porous matrix is mounted to the distal end of the catheter shaft; and

Fig. 8 illustrates a further alternative using TMR so that the channels are formed completely through the

myocardium from the epicardium, and illustrating the administration of a drug into the channels by various means.

5 DESCRIPTION OF THE PREFERRED EMBODIMENT

Fig. 1 illustrates a catheter assembly 2 made according the invention. Catheter assembly 2 comprises a catheter 4 having a handle 6, the handle coupled to a laser energy source 8 and a source 10 of an angiogenic factor. The catheter is useful for delivering a variety of active agents to cardiac tissue, particularly angiogenic factors and formulations as described in copending application no. 08/753,224, the full disclosure of which was previously incorporated herein by reference. Catheter 4 also includes a hollow catheter shaft 12 having a proximal end 14 connected to handle 6 and an open distal end 16. The interior catheter shaft 12 houses a set of optical fibers 18 which transmit laser energy from source 8. A central lumen 20 passes along the center of catheter shaft 12 and is used to deliver the angiogenic factor from agent source 10.

Fig. 2 illustrates a heart 22 with a portion of the myocardium 24 broken away to show the interior of the left ventricle 26. The left ventricle is supplied oxygenated blood from the lungs. This figure shows a PMR (percutaneous myocardial revascularization) approach to deliver the angiogenic factor in which distal end 16 of catheter shaft 12 is passed through the aorta 28, across the aortic valve in a retrograde fashion and into the left ventricle 26. Catheter shaft 12 is steerable to permit distal end 16 to be positioned against the endocardium 30 at a plurality of target sites. Once in position adjacent to endocardium 30, laser energy from laser energy source 8 is applied to endocardium 30 to produce an endocardial channel 32. At each position an agent, such as angiogenic factors, is delivered to the endocardial channel 32 through central lumen 20 from agent source 10. In the embodiment of Fig. 1 the angiogenic factor is delivered in a liquid form. As discussed below, the angiogenic factors, or other drug or agent, can be delivered in other forms as well.

Typically, at least 5 channels will be formed, preferably at least 15, and more preferably at least 30, with from 10 to 40 channels being typical.

Depending on the nature of the laser energy source, the catheter 4 may remain outside the myocardium as the channel is formed, as is usually the case with high energy CO₂ lasers. More usually, however, the catheter 4 will penetrate into the myocardium as the channel is being formed, as is the case with moderate energy laser sources, such as holmium: YAG lasers of the type available from Cardiogenesis Corporation, Sunnyvale, California. In a preferred approach, the catheter will penetrate into the myocardium as the laser or other energy is applied to the tissue to create the channel, and the angiogenic factor will be delivered to the tissue immediately following the termination of the energy delivery. Delivery of the angiogenic factor while energy is being delivered is not preferred since the energy would likely degrade the factors and reduce or destroy their activity.

The angiogenic factor promotes the growth of new arterioles 34 illustrated in Fig. 3A and 3B. Arterioles 34 are shown in Fig. 3A as they pass into myocardium 24 and connect with other endocardial channels 32 and extend into the myocardium itself. Fig. 3B illustrates a coronary artery 36 along the epicardium 38 and branches 40 which extend from coronary artery 36 into myocardium 24. Fig. 3B illustrates arterioles 34 extending from channels 32 to coronary arteries 36 and branches 40. Arterioles 34 are shown separately in Figs. 3A and 3B for clarity of illustration. However, it is understood that both type of arteriole growth is expected to occur due to the use of angiogenic factors.

The growth of arterioles 34 is very important to ensure that myocardium 24 is provided with sufficient oxygenated blood to reduce or eliminate the occurrence of myocardial ischemia. Heart 22 in Fig. 2 has already undergone a coronary bypass using bypass grafts 42 as a consequence of blockages, such as blockage 44, in the coronary arteries. Additional partial blockages 46, see Fig. 2, have formed along bypass grafts 42 and along coronary artery 36 at

blockage 47 (Fig. 3B). These additional blockages 46, 47 create myocardial ischemia necessitating additional measures to provide oxygenated blood to myocardium 24. As shown in Figs. 3A and 3B, the growth of arterioles 34 not only provides
5 oxygenated blood into myocardium 24 through endocardial channels 32 but also permits blood along coronary artery 36 to bypass blockage 48 due to the interconnection of arterioles 34 with one another and with coronary artery 36.

Fig. 4 illustrates an alternative embodiment of the invention in which the locations of optical fibers 18 and
10 lumen 20 are reversed compared to Fig. 1. Optical fibers 18 of catheter 4a are located in the center of catheter shaft 12a while a number of axially-extending lumens 20a are situated around fibers 18 adjacent to the periphery of shaft 12a.

Catheter 4b of Fig. 5 is similar to catheter 4 of Fig. 1 with the exception of the use of an extendable hollow
15 needle 49 housed within lumen 20. Needle 49, shown in its extended position in Fig. 5, is extended after laser energy is used to form an endocardial channel 32 but before distal end
20 16 has been moved to ensure proper positioning of the needle into the channel. This embodiment is particularly useful when the catheter 4b is not penetrated into the tissue while energy is delivered.

Fig. 6A illustrates a catheter 4c similar to
25 catheter 4 but having a somewhat enlarged central lumen 20c. This permits catheter 4c to deliver spherical particles 48 through central lumen 20c for delivery into the recently formed endocardial channels 32. Note that in procedures such as PMR it is obligatory to maintain distal end 16 of catheter
30 shaft 12 in position after endocardial channels 32 have been formed to ensure that the agent is properly delivered into the endocardial channels. Where visualization of the channel entrances is not a problem, as in the case of TMR, this restriction may not be necessary. Spherical particles 48 may
35 be biodegradable/bioerodible or bioeluting to provide the angiogenic factors to myocardium 24 over a period of time. Fig. 6A illustrates rod-shaped particles 50 which may be used instead of spherical particles 48. Fig. 6B illustrates

tubules 52 which can be delivered in series through central lumen 20c. Tubules 52 are preferably bioeluting polymeric materials to deliver an angiogenic agent to myocardium 24 over a period of time. Tubules 52 also help to keep endocardial channels 32 from closing and allow blood to traverse their central lumens. Other shapes of particles and elements for delivery of the agent can also be used. For example, instead of tubules 52, a coil construction could be inserted into endocardial channels 32 to both help keep endocardial channels 32 open and minimize the obstruction of the walls of the channels, preferably within 24 hours of the channel formation, more preferably simultaneously with the channel formation. All such particles and elements are referred to collectively as controlled release element herein.

Fig. 7 shows an alternative embodiment in which a catheter 4d is shown to include a solid bundle of optical fibers 18 at its center and a compressible porous matrix 54 extending beyond the distal end 16 of catheter 4d. Porous matrix 54 contains the angiogenic agent so that after endocardial channels 32 are formed, pressing porous matrix 54 against endocardium 30 surrounding channel 32 causes the agent to flow into the channel. The angiogenic agent is provided to porous matrix 54 by a separate fluid feed tube 56 mounted on the outer surface of catheter shaft 12.

Fig. 8 illustrates a further aspect of the invention practiced using a TMR technique. Fig. 8 shows a section of myocardium 24 having myocardial channels 58 formed completely through myocardium 24. Fig. 8 illustrates two different methods for delivering angiogenic agent into channels 58. One way is to use a syringe 60 following the formation of channels 58. This is possible with this type of technique because epicardium 38 is exposed and visible to the physician so that the openings into channels 58 at the epicardium 38 are visible to permit proper placement of syringe needle 62. Syringe needle 62 could also be totally or partially blocked at its distal end and have a set of side openings to allow the agent to be dispensed into the channels. Alternatively, or in addition, a slow-release gel, for example a pluronic gel 64,

can be painted over the openings channels 58 formed in epicardium 38. This permits the slow release of an angiogenic agent into channels 58 as is desired. Instead of gel 64, a time-released patch, not shown, could be used over the openings to channels 58 formed in epicardium 38. Also an agent can be introduced into the pericardial space surrounding the heart after channels have been formed into the epicardium.

As a further alternative, in some cases it may be sufficient to perform TMR and/or PMR to create the desired plurality of channels into the myocardium and then to locally or systemically delivery the angiogenic or other factor to the patient, e.g. by injection, infusion, or the like, preferably within 24 hours of the channel formation, more preferably simultaneously with the channel formation. The angiogenic or other factor can then reach the target myocardial channels through the left ventricle and initiate the desired angiogenesis. Generally, however, this use of system angiogenic factor delivery may be less preferred, because of both reduced delivery to the myocardium and an increased risk of side effects because of the higher amounts of agent that would likely be employed. It will also be possible to deliver the angiogenic or other active agent locally, e.g. intramurally through a coronary artery or vein, concurrently or within 24 hours of the channel forming step. Use of intravascular catheters for such delivery is taught in USSN 08/753,224.

The use of catheter assembly 2 for a PMR procedure proceeds generally as follows. Distal end 16 is passed percutaneously into the vascular system of the patient, through aorta 28, retrograde across the aortic valve, into the left ventricle 26 and to a target site against endocardium 30. Laser energy source 8 is then activated to cause laser energy to exit optical fibers 18 to ablate or burn endocardial channels 32 into myocardium 24. While distal end 16 remains at the newly formed endocardial channel 32, agent source 10 supplies an agent, typically an agent containing an angiogenic factor, into newly formed endocardial channel 32. Distal end 16 is then repositioned to a new target site along endocardium

30 and the process is repeated. By doing so growth of arterioles 34 is promoted as suggested in Figs. 3A and 3B to provide oxygenated blood to myocardium 24 both from left ventricle 26 and typically from coronary artery 36 bypassing blockage 47.

The publications, patents and applications referred to above are all incorporated by reference.

Other modifications and variations can be made to the disclosed embodiments without departing from the subject of the invention as defined in the following claims. For example, channels 32 may be formed, for example, using ultrasound, radio frequency energy, microwave energy, drills or puncturing elements such as needles, in place of or in addition to laser energy.

WHAT IS CLAIMED IS:

1 1. A method for promoting angiogenesis in cardiac
2 tissue, said method comprising:
3 forming a plurality of channels extending at least
4 partly into the myocardium; and
5 delivering an angiogenic factor into the plurality
1 of channels.

1 2. A method as in claim 1, wherein the forming
2 step comprises successively advancing a tissue-penetrating
3 element into the myocardium while delivering the angiogenic
4 factor therethrough.

1 3. A method as in claim 2, wherein the advancing
2 step is repeated at least 5 times.

1 4. A method as in claim 2, wherein the channels
2 remain patent after they are formed.

1 5. A method as in claim 2, wherein the advancing
2 step comprises advancing the tissue-penetrating element from
3 the epicardium through the myocardium into the left ventricle.

1 6. A method as in claim 2, wherein the advancing
2 step comprises advancing the tissue-penetrating element from
3 the left ventricle through the endocardium and into the
4 myocardium.

1 7. A method as in claim 6, wherein the tissue-
2 penetrating device is further advanced through the epicardium.

1 8. A method as in claim 2, wherein the advancing
2 step comprises applying energy from a distal tip of the
3 tissue-penetrating element to remove tissue as the element
4 advances.

1 9. A method as in claim 8, wherein the energy
2 applying step comprises applying at least one of laser energy,
3 ultrasound energy, radio frequency energy, and microwave
4 energy.

1 10. A method as in claim 1, wherein the angiogenic
2 factor is delivered locally to an endocardial surface, and
3 epicardial surface, or through the coronary vasculature.

1 11. A method as in claim 1, wherein the angiogenic
2 factor is delivered within 24 hours of forming the channels.

1 12. A method as in claim 1, wherein the angiogenic
2 factor is delivered systemically so that it is present in the
3 left ventricle while or within 24 hours of forming the
4 channels.

1 13. A method as in claim 1, wherein the angiogenic
2 factor is selected from the group consisting of vascular
3 endothelial growth factor, acidic fibroblast growth factor,
4 and basic fibroblast growth factor.

1 14. A method for delivering an active agent to
2 cardiac tissue said method comprising:
3 advancing a tissue-penetrating element into the
4 cardiac tissue a plurality of times; and
5 delivering the active agent through the tissue-
6 penetrating element.

1 15. A method as in claim 14, wherein the tissue-
2 penetrating element is advanced at least 5 times.

1 16. A method as in claim 14, wherein the advancing
2 step comprises advancing the tissue-penetrating element from
3 the epicardium through the myocardium into the left ventricle.

1 17. A method as in claim 14, wherein the advancing
2 step comprises advancing the tissue-penetrating element from
3 the left ventricle through the endocardium and into the
4 myocardium.

1 18. A method as in claim 17, wherein the tissue-
2 penetrating device is further advanced through the epicardium.

1 19. A method as in claim 14, wherein the advancing
2 step comprises applying energy from a distal tip of the
3 tissue-penetrating element to remove tissue as the element
4 advances.

1 20. A method as in claim 19, wherein the energy
2 applying step comprises applying at least one of laser energy,
3 ultrasound energy, radio frequency energy, and microwave
4 energy.

1 21. A method as in claim 20, wherein the active
2 agent is selected from the group consisting of polypeptides,
3 carbohydrates, nucleic acids, gene vectors, and genetically
4 modified cells.

1 22. A method as in claim 14, wherein the active
2 agent is present in a controlled release element.

1 23. A system for delivering an active agent to
2 cardiac tissue, said system comprising:
3 a catheter having an energy-applying distal tip
4 adapted to penetrate tip adapted to penetrate cardiac tissue
5 and form a channel extending from the endocardium at least
6 partly into the myocardium, said element having at least one
7 lumen therethrough; and
8 a reservoir containing the active agent and
9 connected to said catheter so that said angiogenic factor can
10 be delivered to the cardiac tissue through the lumen.

1 24. A system as in claim 23, wherein the catheter
2 comprises optical fibers extending axially therethrough for
3 applying energy from the distal tip.

1 25. A system as in claim 24, wherein the lumen and
2 the axial fibers are arranged concentrically.

1 26. A system as in claim 25, wherein the optical
2 fibers are arranged concentrically about the lumen.

1 27. A system as in claim 26, wherein the lumen is
2 arranged annularly about the optical fibers.

1 28. A system as in claim 23, wherein the active
2 agent comprises an angiogenic factor is selected from the
3 group consisting of vascular endothelial growth factor, acidic
4 fibroblast growth factor, and basic fibroblast growth factor.

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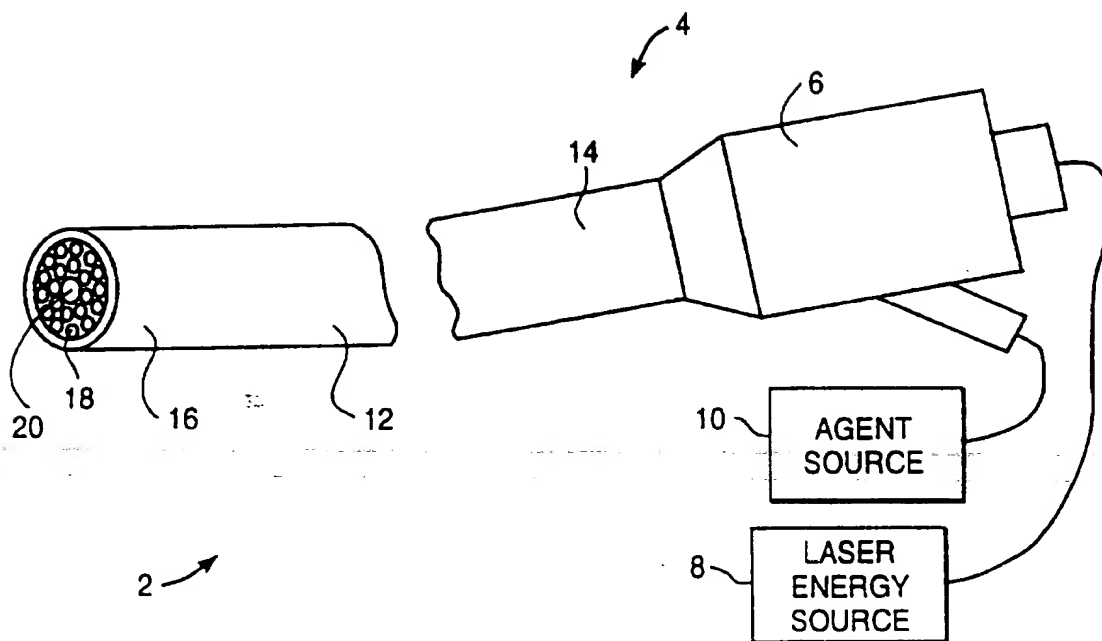


FIG. 1

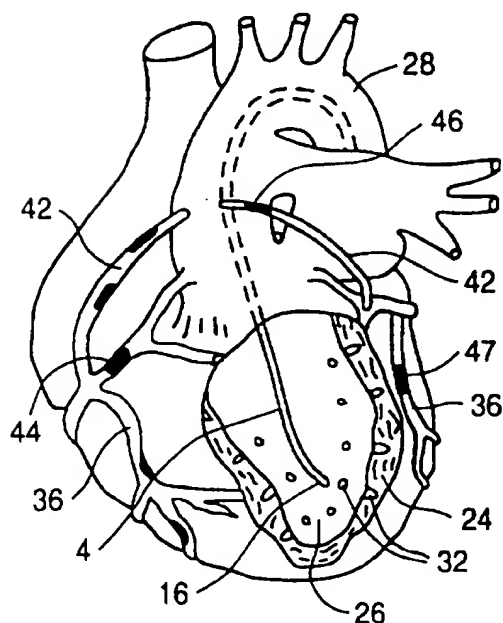


FIG. 2

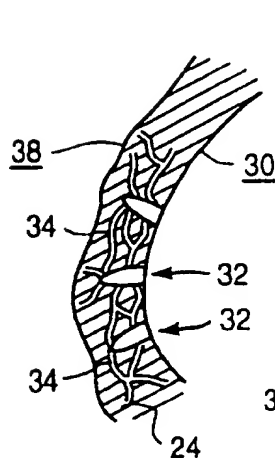


FIG. 3A

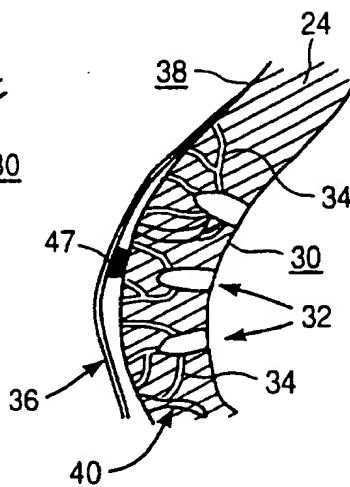


FIG. 3B

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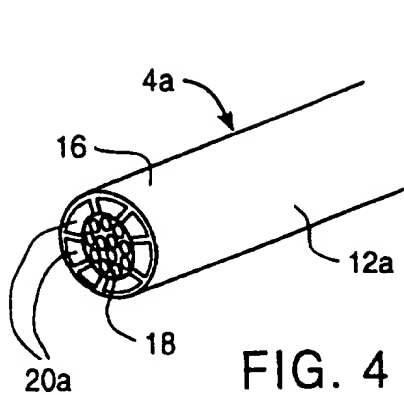


FIG. 4

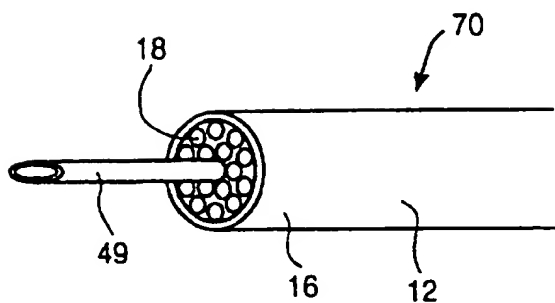


FIG. 5

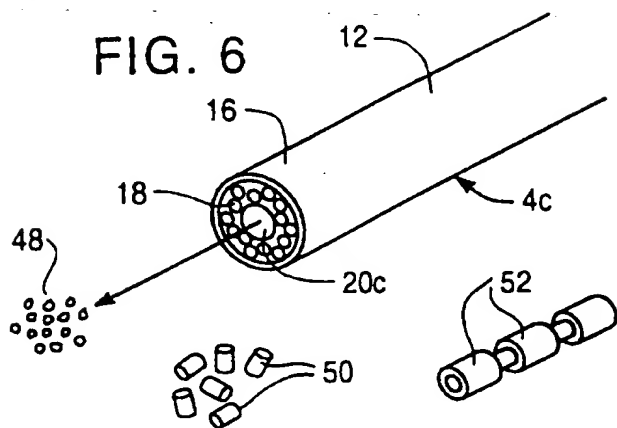


FIG. 6A

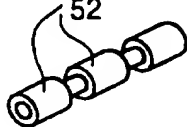


FIG. 6B

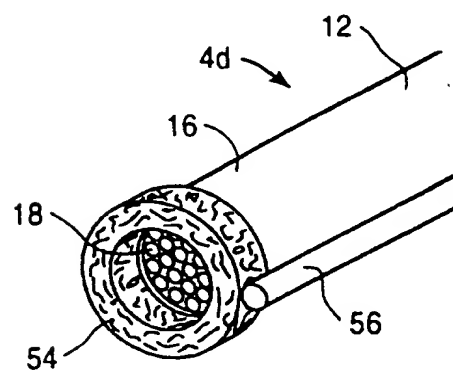


FIG. 7

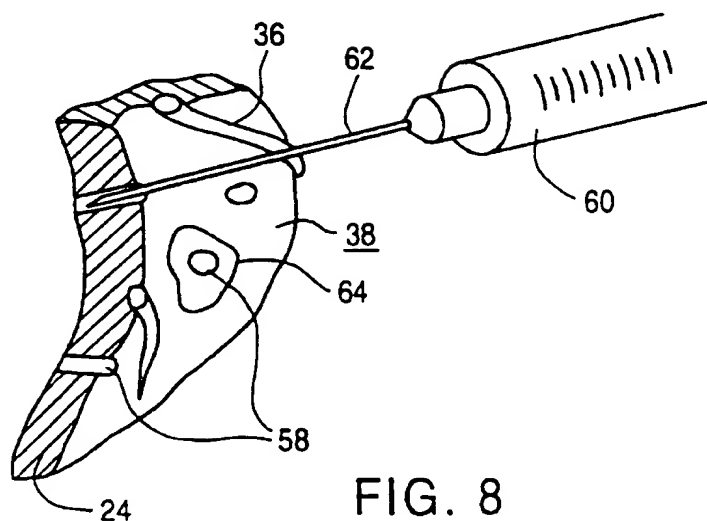


FIG. 8

SUBSTITUTE SHEET (RULE 26)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US97/13904

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :A61K 9/22

US CL :604/890.1

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 604/20, 49; 607/89, 93

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

APS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 5,269,326 A (VERRIER) 14 December 1993, figures, col. 4 paragraph 2, 7 and 8,	1-28
X	US 5,330,467 A (ABELA) 19 July 1994, Abstract, figures, col. 2 paragraphs 7 and 8, col. 4, paragraphs 2, 4 and 5, col. 5 paragraph 3, and col. 6 paragraph 4.	14, 19, 23, 24-27
&	US 5,586,982 A (ABELA) 24 December 1996.	1-28



Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents:

A document defining the general state of the art which is not considered to be of particular relevance

E earlier document published on or after the international filing date

L document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

O document referring to an oral disclosure, use, exhibition or other means

P document published prior to the international filing date but later than the priority date claimed

T

later document published after the international filing date or priority date and not in conflict with the application but cited to underpin the principle or theory underlying the invention

X

document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

Y

document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

A

document member of the same patent family

Date of the actual completion of the international search

03 DECEMBER 1997

Date of mailing of the international search report

05 JAN 1998

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